

WE CLAIM:

1. A method of screening a test agent for hepatotoxicity, the method comprising;
 - (a) providing a test cell population comprising a cell capable of expressing one or more nucleic acid sequences selected from the group consisting of RISKMARKER 1-8 and INJURYMARKER 1-10;
 - (b) contacting the test cell population with a test agent;
 - (c) measuring expression of one or more of the nucleic acid sequences in the test cell population;
 - (d) comparing the expression of the nucleic acid sequences in the test cell population to the expression of the nucleic acid sequences in a reference cell population comprising at least one cell whose exposure status to a hepatotoxic agent is known; and
 - (e) identifying a difference in expression levels of the RISKMARKER or INJURYMARKER sequences, if present, in the test cell population and reference cell population,thereby screening said test agent for hepatotoxicity.
2. The method of claim 1, wherein said hepatotoxicity comprises idiosyncratic hepatotoxicity.
3. The method of claim 2, wherein the method comprises comparing the expression of one or more nucleic acid sequences selected from the group consisting of RISKMARKER 1-8.
4. The method of claim 2, wherein the method comprises comparing the expression of one or more nucleic acid sequences selected from the group consisting of INJURYMARKER 1-10.
5. The method of claim 1, wherein the method comprises comparing the expression of 6 or more of the nucleic acid sequences.

6. The method of claim 1, wherein the expression of the nucleic acid sequences in the test cell population is decreased as compared to the reference cell population.
7. The method of claim 1, wherein the expression of the nucleic acid sequences in the test cell population is increased as compared to the reference cell population.
8. The method of claim 1, wherein the test cell population is provided in vitro.
9. The method of claim 1, wherein the test cell population is provided ex vivo from a mammalian subject.
10. The method of claim 1, wherein the test cell population is provided in vivo in a mammalian subject.
11. The method of claim 1, wherein the test cell population is derived from a human or rodent subject.
12. The method of claim 1, wherein the test cell population includes a hepatocyte.
13. The method of claim 1, wherein said test agent is an idiosyncratic hepatotoxic agent.
14. The method of claim 1, wherein said test agent is a non-steroidal anti-inflammatory drug (NSAID).
15. The method of claim 3, wherein said hepatotoxic agent is a NSAID.
16. The method of claim 15, wherein said NSAID is a NSAID classified as having a low risk of hepatotoxicity, and wherein said test agent is identified as having a low risk of hepatotoxicity if no qualitative difference in expression levels is identified in step (e).

17. The method of claim 16, wherein said difference in expression levels is determined by comparing expression transformation eigenvectors for said test cell and reference cell populations.
18. The method of claim 16, wherein said NSAID is selected from the group consisting of Benoxaprofen, Bromfenac, Diclofenac, Phenylbutazone, and Sulindac.
19. The method of claim 18, wherein said NSAID is selected from the group consisting of Benoxaprofen, Phenylbutazone, and Sulindac.
20. The method of claim 15, wherein said NSAID is a NSAID classified as having a very low risk of hepatotoxicity, and wherein said test agent is identified as having a very low risk of hepatotoxicity if no qualitative difference in expression levels is identified in step (e).
21. The method of claim 20, wherein said difference in expression levels is determined by comparing expression transformation eigenvectors for said test cell and reference cell populations.
22. The method of claim 20, wherein said NSAID is selected from the group consisting of Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamate, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Suprofen, Tenoxicam, Tolmentin, and Zomepirac.
23. The method of claim 22, wherein said NSAID is selected from the group consisting of Flurbiprofen, Oxaprozin, and Tenoxicam.
24. The method of claim 15, wherein said NSAID is a NSAID classified as having an overdose risk of hepatotoxicity, and wherein said test agent is identified as having an overdose risk of hepatotoxicity if no qualitative difference in expression levels is identified in step (e).

25. The method of claim 24, wherein said difference in expression levels is determined by comparing expression transformation eigenvectors for said test cell and reference cell populations.
26. The method of claim 25, wherein said NSAID is selected from the group consisting of Acetaminophen, Acetylsalicylic acid, and Phenacetin.
27. The method of claim 4, wherein said hepatotoxic agent is a NSAID.
28. The method of claim 27, wherein said NSAID is a NSAID classified as inducing hepatocellular damage, and wherein said test agent is identified as likely to induce hepatocellular damage if no qualitative difference in expression levels is identified in step (e).
29. The method of claim 28, wherein said difference in expression levels is determined by comparing expression transformation eigenvectors for said test cell and reference cell populations.
30. The method of claim 27, wherein said NSAID is selected from the group consisting of Acetaminophen, Flurbiprofen, and Ketoprofen.
31. The method of claim 27, wherein said NSAID is a NSAID classified as inducing cholestasis, and wherein said test agent is identified as likely to induce cholestasis if no qualitative difference in expression levels is identified in step (e).
32. The method of claim 31, wherein said difference in expression levels is determined by comparing expression transformation eigenvectors for said test cell and reference cell populations.

33 The method of claim 30, wherein said NSAID is selected from the group consisting of Benoxaprofen, Nabumetone, and Sulindac.

34. The method of claim 27, wherein said NSAID is a NSAID classified as inducing elevated transaminase level, and wherein said test agent is identified as likely to induce elevated transaminase level if no qualitative difference in expression levels is identified in step (e).

35. The method of claim 34, wherein said difference in expression levels is determined by comparing expression transformation eigenvectors for said test cell and reference cell populations.

36. The method of claim 34, wherein said NSAID is selected from the group consisting of Zomepirac, Mefenamic acid, and Tenoxicam.

37. A method of assessing the hepatotoxicity of a test agent in a subject, the method comprising:

(a) providing from the subject a test cell population comprising a cell capable of expressing one or more nucleic acid sequences selected from the group consisting of RISKMARKER 1-8 and INJURYMARKER 1-10;

(b) contacting the test cell population with a test agent;

(c) measuring expression of one or more of the nucleic acid sequences in the test cell population; and

(d) comparing the expression of the nucleic acid sequences in the test cell population to the expression of the nucleic acid sequences in a reference cell population comprising at least one cell whose exposure status to a hepatotoxic agent is known;

(e) identifying a difference in expression levels of the nucleic acid sequences, if present, in the test cell population and the reference cell population, thereby assessing the hepatotoxicity of the test agent in the subject.

38. The method of claim 37, wherein said hepatotoxicity comprises idiosyncratic hepatotoxicity.
39. The method of claim 38, wherein the method comprises comparing the expression of one or more nucleic acid sequences selected from the group consisting of RISKMARKER 1-8.
40. The method of claim 38, wherein the method comprises comparing the expression of one or more nucleic acid sequences selected from the group consisting of INJURYMARKER 1-10.
41. The method of claim 37, wherein the expression of the nucleic acid sequences in the test cell population is increased as compared to the reference cell population.
42. The method of claim 37, wherein the expression of the nucleic acid sequences in the test cell population is increased as compared to the reference cell population.
43. The method of claim 37, wherein said subject is a human or rodent.
44. The method of claim 37, wherein the test cell population is provided ex vivo from said subject.
45. The method of claim 37, wherein the test cell population is provided in vivo from said subject.
46. The method of claim 37, wherein said test agent is a non-steroidal anti-inflammatory drug (NSAID).
47. The method of claim 37, wherein said hepatotoxic agent is a NSAID.

Sub 25 48-
A1
An isolated nucleic acid comprising a nucleic acid sequence selected from the group consisting of a RISKMARKER 1 nucleic acid, a RISKMARKER 6-8 nucleic acid, and their complements.

49. A vector comprising the nucleic acid of claim 48.

50. A cell comprising the vector of claim 49.

51. A pharmaceutical composition comprising the nucleic acid of claim 48.

52. A polypeptide encoded by the nucleic acid of claim 48.

53. An antibody which specifically binds to the polypeptide of claim 52.

54. A kit which detects two or more of the nucleic acid sequences selected from the group consisting of RISKMARKER 1, and RISKMARKER 6-8.

55. An array which detects one or more of the nucleic acid selected from the group consisting of RISKMARKER 1, and RISKMARKER 6-8.

56. A plurality of nucleic acid comprising one or more of the nucleic acid selected from the group consisting of RISKMARKER 1, and RISKMARKER 6-8.

add B1